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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/486,167	08/15/2000	Bernard Knoops	VANM143.001A	2578

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/486,167	KNOOPS ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/24/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9 and 12-32* is/are pending in the application.

4a) Of the above claim(s) *13,15 and 17-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9,12,14,16 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/24/02 has been entered.

2. Claims 5, 9, and 12-32 are pending.

3. Claims 13, 15, and 17-31 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 5, 9, 12, 14, 16 and 32, drawn to nucleic acid, vector, host cell, pharmaceutical composition and diagnostic device comprising said nucleic acid are being acted upon in this Office Action.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/or Amino Acid Sequence Disclosure.

   This application fails to comply with the sequence rules because SEQ ID NO is required for the primers on page 18 at line 27; it is noted that SEQ ID NOS have been deleted in the newly submitted paragraph in the amendment filed 12/24/02. Appropriate correction is required.

6. The specification stands objected to because of the following informalities: (1) "(MIN **n°**147050)" on page 20 at line 23, (2) "high bone mass syndrome (MIN **n°**601884)" on page 20 at line 24, (3) "Osteopetrosis (MIN **n°**259700)" on page 20 at line 25, (4) "Osteoporosis-pseudoglioma syndrome (MIM **n°**259770)" and "Bardet-Biedl syndrome 1 (MIM **n°**209901" on page 20 at line 27. All **n°** mentioned above should have been No. It is noted that the amendment

to the specification on page 20 at line 25 filed on 12/24/02 is incorrect. It should have been on page 20, line 24 and **not** at line 25. Appropriate correction is required.

7. The drawings, filed 8/15/00, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review mailed 11/6/01. Appropriate action is required.

8. Claims 14 and 32 are objected to because it drawn to a peptide, which is a non-elected invention.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 5, 9, 12, 14, 16 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) two human polynucleotides consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encode a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, respectively, and polynucleotide probes of SEQ ID NOS: 7-9, and 11-16 (See page 7 of the specification) for in vitro diagnosis, **does not** reasonably provide enablement for (1) *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (2) any vector comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (3) any diagnostic device comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (4) *any* "pharmaceutical" composition comprising a pharmaceutical acceptable carrier and *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand or any peptide encoded by *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1, (5) *any* cell transformed by the vector comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, and (6) *any* "pharmaceutical" composition comprising a pharmaceutical acceptable carrier and the polynucleotide "consisting of essentially of" SEQ ID NO: 1" or its complementary strand further comprising *any* purified antibody or *any* "active portion" of said antibody that specifically binds a polypeptide encoded by said nucleotide sequence for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a human polynucleotide (cDNA) consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 encoding a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, from human, rat and mouse, respectively, (2) polynucleotide probes of SEQ ID NOS: 7-9 for in vitro diagnosis or monitoring lung injury associated with oxidative stress-related disorder.

The specification does not provide any guidance as how to use *any* polynucleotide mentioned above for a pharmaceutical composition for treating *any* disease because the specification and the claims as originally filed do not support for the term "consisting essentially of". Thus there is no guidance as to the structural length of the claimed polynucleotide because the term "consisting essentially of" is still open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. Not only there is no guidance as to the length of polynucleotide sequence, there are also no *in vivo* working examples to demonstrate that any gene therapy using any pharmaceutical composition comprising the claimed polynucleotide sequence would be effective for treating *any* disease. A "pharmaceutical composition" comprises a "polynucleotide sequence encoding a peptide for treating any diseases in the absence of *in vivo* data is unpredictable for the following reasons: (1) efficacy of the gene therapy using the polynucleotide has not been definitively demonstrated; (2) it is not always possible to extrapolate directly from in vitro diagnostic experiments to in vivo treatment of any disease; (3) the enhancing or maintaining high level expression of genes transferred to somatic cells may not persist or consistently achieved; (4) the appropriate expression of polynucleotide transfer to specific cell types (target specificity) has not been demonstrated; (5) adverse reactions from the recipient may result; (6) the lower efficiency of gene transfer (naked nucleic acid) compared with viruses and the effective therapeutic amount have not been addressed.

Das *et al* (of record) teach that getting the antisense to the cell nuclei where their anti-gene action can take place can be difficult (See abstract, in particular).

Verma *et al* (of record) teach that the problem of gene therapy is the inability to deliver genes efficiently to the right type of cell, obtaining sustained expression of the therapeutic protein and without triggering the host immune responses (See page 239, in particular). Therefore, in the absence of in vivo working examples, it would require undue experimentation of one skilled in the art to practice the claimed invention.

With regard to claim 32, there is insufficient guidance as to the binding specificity of a purified antibody such as the antigenic determinant of the purified antibody or the epitope on the polypeptide encoded by the nucleotide of SEQ ID NO: 1 to which the antibody binds in a pharmaceutical composition as set forth in claim 32. Further, there is no guidance as to which "portion" of the antibody is considered to be "active". The specification does not disclose a pharmaceutical composition comprising a polynucleotide and an antibody as set forth in claim 32 for treating any disease. Again, there are no in vivo working examples in the specification as filed to demonstrate that the claimed pharmaceutical composition is effective for treating any disease. In the absence of guidance and working example, it is unpredictable which undisclosed pharmaceutical composition is useful for treating which disease. As such, further research would be required to practice the claimed invention. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/24/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 5 has been amended to recite an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand, which clearly enabled by the specification. (2) The inventors have demonstrated that the systemic administration of recombinant peroredoxin 5 to mice induced a dose-dependent neuroprotection

against excitotoxic brain lesions. Recombinant PRDX5 (0.1-20 mg/kg) was administered by interperitoneal injection (page 4). (3) Applicants also submit a copy of a paper entitled "Ovorexpression of human peroxiredoxin 5 in Chinese Hamster Ovary cells: effect on cell survival and DNA damage during acute oxidative stress induced by peroxides". In this paper, overexpressing PRDX5 by stably transfected with a vector comprising the cDNA sequence of PRDX5 in either cytosolic or mitochondrial compartments significantly reduced cell death

In response to Applicants' argument in item 1, the term "consisting essentially of" has no support in the specification or the claims as originally filed and now change the scope of the claimed polynucleotide. This is new matter and requires removal.

In response to Applicants' argument in item 2, claims 5, 9, 12, 14, 16 and 32 are drawn to nucleotides and not polypeptide. The pharmaceutical composition comprising the polynucleotide is equivalent to gene therapy and this is clearly not enabled for the reasons of record (See rejection supra). The Office Action mailed November 16, 2001 clearly states that the specification, while being enabling for (1) two human polynucleotides consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encode a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, respectively, and polynucleotide probes of SEQ ID NOS: 7-9, and 11-16 (See page 7 of the specification) for in vitro diagnosis, does not enable for a pharmaceutical composition comprising polynucleotide of SEQ ID NO: 1. The said Office Action does not indicate that the inventors have demonstrated that the systemic administration of recombinant peroxiredoxin 5 (PRDX5) to mice induced a dose-dependent neuroprotection against excitotoxic brain lesions. The instant specification has no in vivo working example, let alone administering recombinant peroxiredoxin 5 (PRDX5) to mice. Even if the inventors have demonstrated that the systemic administrations of recombinant peroxiredoxin 5 (PRDX5), which is a protein or polypeptide, to mice and induced a dose-dependent neuroprotection against excitotoxic brain lesions, it is irrelevant for instant claims which drawn to polynucleotide, let alone gene therapy (pharmaceutical composition comprising a polynucleotide).

In response to Applicants' argument in item 3, in vitro transfection assay is quite different than in vivo treatment using polynucleotide (that reads on gene therapy), let alone treating *any* disease. There is no showing in the specification as filed that the claimed polynucleotide is stably expressed in the subcellular compartment such as the cytosol or the mitochondria of the right cell type within the particular tissue of the animal. There are also no *in*

vivo working examples demonstrating that the claimed "pharmaceutical" composition would be effective for treating *any* disease. A "pharmaceutical composition" comprises a "polynucleotide sequence encoding a peptide for treating any diseases in the absence of *in vivo* data is unpredictable for the following reasons: (1) efficacy of the gene therapy using the polynucleotide has not been definitively demonstrated; (2) it is not always possible to extrapolate directly from in vitro diagnostic experiments to in vivo treatment of any disease; (3) the enhancing or maintaining high level expression of genes transferred to somatic cells may not persist or consistently achieved; (4) the appropriate expression of polynucleotide transfer to specific cell types (target specificity) has not been demonstrated; (5) adverse reactions from the recipient may result; (6) the lower efficiency of gene transfer (naked nucleic acid) compared with viruses and the effective therapeutic amount have not been addressed.

11. Claims 5, 9, 12, 14, 16 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for a cell transformed by *any* vector comprising (1) *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (2) any vector comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (3) any diagnostic device comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, (4) *any* "pharmaceutical" composition comprising a pharmaceutical acceptable carrier and *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand or any peptide encoded by *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1, (5) *any* cell transformed by the vector comprising *any* polynucleotide "consisting of essentially of" SEQ ID NO: 1 or its complementary strand, and (6) *any* "pharmaceutical" composition comprising a pharmaceutical acceptable carrier and the polynucleotide "consisting of essentially of" SEQ ID NO: 1" or its complementary strand further comprising *any* purified antibody or *any* "active portion" of said antibody that specifically binds a polypeptide encoded by said nucleotide sequence for treating *any* disease.

The specification discloses only (1) a human polynucleotide (cDNA) consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID

NO: 5 encoding a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, from human, rat and mouse, respectively, (2) polynucleotide probes of SEQ ID NOS: 7-9 for in vitro diagnosis or monitoring lung injury associated with oxidative stress-related disorder.

There is a lack of a written description about the structure associated with function of *any* polynucleotide mentioned above "consisting essentially of" SEQ ID NO: 1 because term "consisting essentially of" is still open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. There is inadequate written description about the undisclosed polynucleotides to be added. Further, the specification and the claims as originally filed do not provide a clear support for said phrase. Applicants have not pointed out the support for "consisting essentially of" comes from.

With regard to a pharmaceutical composition comprising a polynucleotide "consisting essentially of" SEQ ID NO: 1, there is insufficient written description about the disease to be treated by said pharmaceutical composition given the indefinite number of diseases to be treated with said pharmaceutical composition. Further, the specification merely states a pharmaceutical composition comprising a polynucleotide of SEQ ID NO: 1. The specification does not describe a pharmaceutical composition as set forth in claim 32. There is a lack of written description about the binding specificity of a purified antibody. Further, there is insufficient written description about which "portion" of the antibody is considered to be "active", much less treating any disease using a pharmaceutical composition comprising a polynucleotide or a polynucleotide and an antibody or an active portion of an antibody.

Given the lack of a written description of any pharmaceutical composition comprising a polynucleotide for treating any disease, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/24/02 have been fully considered but are not found persuasive.

Applicants' position is that claim 5 has been amended to recite an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand, and applicants assert that the presently claimed invention is disclosed in the specification as filed.

In response, the term "consisting essentially of" has no support in the specification or the claims as originally filed. This is new matter and requires removal. There is a lack of a written description about the structure associated with function of *any* polynucleotide mentioned above "consisting essentially of" SEQ ID NO: 1 because term "consisting essentially of" is still open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. There is inadequate written description about the undisclosed polynucleotides to be added. Further, the specification and the claims as originally filed do not provide a clear support for said phrase. Applicants have not pointed out the support for "consisting essentially of" comes from.

With regard to a pharmaceutical composition comprising a polynucleotide "consisting essentially of" SEQ ID NO: 1, there is insufficient written description about the disease to be treated by said pharmaceutical composition given the indefinite number of diseases to be treated with said pharmaceutical composition. Further, the specification merely states a pharmaceutical composition comprising a polynucleotide of SEQ ID NO: 1. The specification does not describe a pharmaceutical composition as set forth in claim 32. There is a lack of written description about the binding specificity of a purified antibody. Further, there is insufficient written description about which "portion" of the antibody is considered to be "active", much less treating any disease using a pharmaceutical composition comprising a polynucleotide or a polynucleotide and an antibody or an active portion of an antibody.

12. Claims 5, 9, 12, 14, 16 and 32 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "consisting essentially of" in Claim 5 represents a departure from the specification and the claims as originally filed because said phrase has no support in the claims and the specification as originally filed and now it changes the scope of the claimed polynucleotide. Further, applicants have not pointed out the support for said phrase in the amendment filed 12/24/02.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
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March 10, 2003

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